BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problems Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 91/17744
A61K 9/22, 9/52, A61L 27/00	A1	(43) International Publication Date: 28 November 1991 (28.11.91)

(21) International Application Number: PCT/US91/02784

(22) International Filing Date: 23 April 1991 (23.04.91)

(30) Priority data:

523,067	14 May 1990 (14.05.90)	US
599,699	18 October 1990 (18.10.90)	US

(71)(72) Applicant and Inventor: JERNBERG, Gary, R. [US/US]; 99 Navaho Avenue, Suite 102, Mankato, MN 56001 (US).

(74) Agent: SCHUMANN, Michael, D.; Merchant, Gould, Smith, Edell, Welter & Schmidt, 3100 Norwest Center/90 South Seventh Street, Minneapolis, MN 55402 (US).

(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SURGICAL IMPLANT AND METHOD INCORPORATING CHEMOTHERAPEUTIC AGENTS

(57) Abstract

An implant and method is disclosed using microparticles to provides a controlled, sustained release, and improved cellular uptake, of chemotherapeutic agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

SURGICAL IMPLANT AND METHOD INCORPORATING CHEMOTHERAPEUTIC AGENTS

Technical Field of the Invention

The present invention relates to a surgical implant and method which provides for controlled release and improved cellular uptake of chemotherapeutic agents over a predetermined period of time.

Background of the Invention

Biologically compatible materials capable of being formed into implants are increasing in use in surgery and medicine. Examples include vascular grafts, ligament prostheses and reconstructive patches.

Utilization of surgical implants presents several problems to the practitioner. For example, the potential of infections exists with surgically placed implants, including grafts, prostheses, etc. See e.g., E. J. Young and B. Sugarman, Infections in Prosthetic Devices, 68 Surg.Clin. N. Am., 167 (1988); The International Journal of Periodontics and Restorative Dentistry, April (1988); B. Van der Lei, et al., Expanded Polytetrafluoroethylene Patch for the Repair of Large Abdominal Wall Defects, 76 Br. J.Surg., 803 (1989); N. S. Horbach, et al., A Suburethral Sling Procedure with Polytetrafluoroethylene for the Treatment of Genuine Stress Incontinence in Patients with low Urethral Closure Pressure, 71 Obstete. Gynecol., 648 (1988).

Adverse clotting problems can also occur with vascular grafts. N. A. Shoenfeld, et al., A New Primate Model for the Study of Intravenous Thrombotic Potential and its Modification, 8 J. Vasc. Surg., 49 (1988); L. J. Dacey, et al., Intraarterial 9-beta-methyl carbacyclin Improves Canine Polytetrafluoroethylene Graft Patency, 8 J. Vasc. Surg., 21 (1988).

Potential infection and excessive inflammation can create problems with orthopedic prostheses. See

e.g., E. J. Young and B. Sugarman, supra; S. P. F. Hughes, Treatment of Infected Implants, Antibiotic Acrylic Composites, 16 Orthopaedic Review, 233 (1987); J. H. Roth, et al., Synovial Reaction Associated with Disruption of Polypropylene Braid-augmented Intraarticular Anterior Cruciate Ligament Reconstruction, 16 Am.J. Sports Med., 301 (1988); S. K. Ahlfeld, et al., Anterior Cruciate Reconstruction in the Chronically Unstable Knee using an Expanded Polytetrafluoroethylene (PTFE) Prosthetic Ligament, 15 Am.J. Sports Med., 326 (1987).

Accordingly, the "take" of these implants, such as a cruciate ligament prosthesis, is variable.

Chemotherapeutic agents have been previously incorporated into vascular grafts. For example, U.S. Patent No. 4,321,711 discloses a vascular prosthesis comprising porous tubing of polytetrafluoroethylene containing an anti-coagulant substance with a porous elastomer coating, containing a substance which counteracts the anti-coagulant, bonded to its outside surface . Typically, the anti-coagulant substance is heparin. Any heparin antagonist such as protamine may be used in the elastomer coating to counteract the heparin. U.S. Patent No. 4,816,339 also refers to the use of therapeutically active substances, such as heparin or antibiotics, placed into an elastomer solution which surrounds a luminal polytetrafluoroethylene layer. However, the incorporated chemotherapeutic agents are soon exhausted from these implants, resulting in renewed potential for clotting. Thus, neither of these inventions provide for the sustained, controlled release of chemotherapeutic agents, nor the enhanced cellular uptake of these agents, that the present invention would provide.

The present invention solves these and many other problems associated with surgical implantation, successful grafting and tissue regeneration.

Summary of the Inv ntion

The present invention relates to a method of sustained, controlled delivery and enhanced uptake of microencapsulated chemotherapeutic and optional carrier agents incorporated into implants to localized treatment sites and tissues in a human or animal body. Also, implants incorporating microencapsulated chemotherapeutic agents and optional carrier agents are provided.

Accordingly, an advantage of one embodiment of the method of the present invention is to provide vascular grafts incorporating microencapsulated chemotherapeutic and optional carrier agents which upon implantation provide for sustained, controlled delivery and improved cellular uptake of anticoagulant agents at the implantation site such that the formation of blood clots (thrombi) are prevented. In addition, microencapsulated chemotherapeutic agents which act as an antagonist to the anticoagulant may be incorporated into an outer layer of the vascular graft.

An advantage of yet another embodiment is to provide prostheses incorporating microencapsulated chemotherapeutic agents and optional carrier agents, including for example, cruciate ligament prostheses, which upon implantation provide for sustained, controlled delivery and improved cellular uptake of antibiotic, anti-inflammatory and other appropriate agents to the implantation site, such that the retention of said prostheses is improved.

These and various other advantages and features of novelty which characterize the invention are pointed out with particularity in the claims annexed hereto and forming a part hereof. However, for a better understanding of the invention, its advantages, and objects attained by its use, reference should be had to the drawings which form a further part hereof, and to the accompanying descriptive matter, in which there is

illustrated and described a preferred embodiment of the invention.

Brief Description of the Drawings

In the drawings, in which like reference numerals and letters indicate corresponding parts throughout the several views,

Figures 1A through 1D are diagrammatic perspective views of alternate configurations of microparticles which might be used in the present invention to contain chemotherapeutic agents or carrier agents;

Figures 2A through 2C are diagrammatic sectional views of alternate embodiments of microparticles having a somewhat spherical configuration with outside walls of varying thicknesses so as to provide for different timed release of chemotherapeutic or carrier agents from inside the microparticles;

Figure 3 illustrates an example of a prior art vascular graph generally according to U.S. Patent No. 4,321,711;

Figures 4A through 4D are end sectional views of vascular grafts illustrating alternate embodiments of vascular grafts showing various methods of incorporation of the microparticles into the vascular grafts;

Figure 5 illustrates an embodiment of a cruciate ligament prosthesis incorporating microencapsulated chemotherapeutic and optional carrier agents in accordance with the principles of the present invention;

Figures 6A,B are an enlarged sectional view of a fiber bundle of the ligament prosthesis shown in Figure 5, illustrating incorporation of the microencapsulated chemotherapeutic and optional carrier agents;

Figures 7A through 7D illustrate representative time release patterns of various chemotherapeutic agents

which might be obtained by the appropriate microparticle configuration, microparticle arrangement in the implant, and chemotherapeutic agents used.

Detailed Description of the Invention

Referring now to Figures 1A-1D, time-release microparticles 10 containing chemotherapeutic and optional carrier agents 12, and incorporated into the matrix of the implants, including, but not limited to, grafts, prostheses, etc., of the present invention can occur in a variety of shapes and sizes.

The microparticles shown in Figures 1A-1D are greatly enlarged, and in actual use, might typically be less than a millimeter in size. As used herein, microparticles broadly include, without limitation, microspheres 14 (hollow and nonhollow), microfibers or microfibrils 16, hollow microfibers 18, microsponges 20, as well as any other microshape which incorporate chemotherapeutic and optional carrier agents into their body or matrix. An outer shell 22 of the microspheres 14 and the microfibers 16, an outer wall 24 of the hollow microspheres 14 and hollow microfibers 18, or matrix 26 of the microsponge 20 is composed of a biodegradable material, thereby allowing for the controlled, sustained release and improved cellular uptake of the chemotherapeutic agents over time.

In one embodiment, the microparticles are incorporated into the microstructure of the material comprising an implant according to the present invention. For example, the microspheres 14 can be contained within the mesh of fine fibrils connecting the matrix of nodes in expanded polytetrafluoroethylene (PTFE). In addition, somewhat larger microspheres can be meshed between layers of a multi-layered PTFE implant structure. The microspheres can be layered within the PTFE implant by adhesively positioning them onto the PTFE or by mixing them with a fluid and/or gel and

flowing them into the netting or weave of the material. In such an embodiment, the fluid and gel can be carrier agents such as hyaluronic acid and a cross-linked gel of hyaluronic acid respectively. Finally, microspheres can also be positioned between the implant and an elastomer coating covering said implants.

In another embodiment, the microfibers or microfibrils can be woven into the mesh of the implant or, as described above, layered between successive layers of PTFE, or a similar material, comprising the implant.

In yet another embodiment, the microparticles may be in the form of microsponges which contain the desired chemotherapeutic and optional carrier agents within their microchanneling.

Microspheres between 10 and 700 microns in diameter are preferred. Various chemical and physical methods for preparing microspheres have been developed over the past twenty-five years and are well known to those skilled in the art. In this regard, see for example Patrick B. Deasy, Microencapsulation and Related Drug Processes. Marcel Dekker Inc., New York, 1984. Coacervation, interfacial polymerization, solvent evaporation and spray drying are examples of methods used in the production of microspheres which incorporate chemotherapeutic and optional carrier agents. Similarly, microfibers or microfibrils can be obtained for layering or weaving into the implant materials of the present invention. In this regard, hollow microfibers ranging in size from 100 to 1,000 microns in diameter can be produced and drug loaded by extrusion.

A wide variety of chemotherapeutic agents can be incorporated into the microshapes employed according to the method of the present invention. For example, antibacterial agents such as the bisbiguanides, antibiotics such as vancomycin or tetracycline, anti-inflammatory agents such as indomethacin or

hydrocortisone, anticoagulants such as heparin and tissue regenerative agents such as fibronectin may be employed, depending upon the particular treatment or preventative goals sought.

Incorporation of the chemotherapeutic and optional carrier agents into the polymer comprising the microshape provides for a slow, sustained release and enhanced cellular uptake of the chemotherapeutic agent. The polymer matrix or carrier material chosen is preferably biodegradable, pharmaceutically acceptable and available in various grades to allow for variable control of the release rate of different chemotherapeutic agents. In this regard, it will be appreciated that the biodegradable materials utilized in time release capsules taken orally or other suitable biodegradable materials safe for use in the body or commonly known may be employed. For example, various biocompatible polymers can be employed, including but not limited to, collagen, cellulosic polymers, ethylene vinyl acetate, methacrylate polymers, lactic-glycolic acid copolymers, polycaprolactone, etc. In addition, polymers such as polystyrene, polycarbonate, polysulfone, polylactides and polyurethane can be employed. It will be appreciated that nonbiodegradable polymers incorporating chemotherapeutic agents are also within the scope of the present invention.

Carrier agents to improve cellular uptake of chemotherapeutic agents can also be incorporated into the implant. In one embodiment, the carrier agents can be mixed with the chemotherapeutic agents for delivery by the microparticles in the previously mentioned configurations. In another embodiment, the carrier agents can be separately incorporated into microparticles, which are then combined with the microparticles incorporating the chemotherapeutic agents. In yet another embodiment, the carrier agents can be in the form of a fluid or gel positioned within

the weave or netting of the implant. In still another embodiment, a cross-linked, polymerized form of the carrier agent can be utilized to form the body of the implant.

Preferred carrier agents include, without limitation, hyaluronic acid, salts thereof such as sodium hyaluronate, esters, ethers, enzymatic derivatives and cross-linked gels of hyaluronic acid and chemically modified derivatives of hyaluronic acid such as hylan. As used herein, hyaluronic acid broadly refers to naturally occurring, microbial and synthetic derivatives of acidic polysaccharides of various molecular weights constituted by residues of D-glucuronic acid and N-acetyl-D-glucosamine.

Referring now to Figures 2A-2C, wherein is illustrated diagrammatic sectional views of alternative embodiments of microspheres in accordance with the present invention. The microspheres 10 have a polymer wall or shell 24 which surrounds the chemotherapeutic and optional carrier agents 12, or matrix containing the chemotherapeutic and optional carrier agents. Thus, the walls of the microspheres may have varying thicknesses and/or be made of a different material to provide for release of the agent continuously or periodically over an extended time period following surgical placement of the implant. For example, an implant may contain an antibiotic which would be released from one type of microparticle during the first critical days following graft placement, whereas an anti-inflammatory agent contained in a second type of microparticle would be released several weeks after implantation. In addition, it is to be understood that the chemotherapeutic and optional carrier agents contained within the microsphere may occur in any appropriate medium, such as aqueous, gelatinous, colloidal or semi-solid media. Furthermore, a carrier agent may also be provided with the microencapsulated chemotherapeutic agent to enhance the

cellular uptake of the chemotherapeutic agent at the desired treatment site.

In another embodiment according to the method of the present invention, the chemotherapeutic and optional carrier agents are positioned at strategic areas of the implants relative to their intended function. For example, an anticoagulant substance could be positioned within the body or internal lining of a vascular graft, while a substance counteracting the anticoagulant would be positioned at the graft outer surface. In addition, a carrier agent can be included to enhance the cellular uptake of the anticoagulant and its antagonist. In a further modification, other chemotherapeutic agents can be positioned at different strategic areas of the implant materials relative to their intended uses. For example, an antibiotic, alone or in conjunction with a carrier agent, could be positioned near the attachment points of a ligament prosthesis, while an anti-inflammatory agent could be positioned within the body of the prosthesis.

Referring now to FIG. 3A, which illustrates a prior art drawing of a vascular graft according to U.S. Patent No. 4,321,711 (Mano). The Mano vascular graft 28 incorporates chemotherapeutic agents, such as the anticoagulant heparin, directly into the body of the vascular graft 30, while incorporating a counteracting substance to the anticoagulant in the elastomer coating surrounding the body of the vascular graft 32.

In comparison, the vascular graft of the present invention may incorporate microencapsulated chemotherapeutic and optional carrier agents into the body of the vascular graft, between the layers comprising the graft or in an elastomer coating surrounding the body of the graft. Thus, in Figures 4A-4D there is illustrated cross-sectional views of vascular grafts 34 incorporating microencapsulated chemotherapeutic and optional carrier agents 10 in

accordance with the method and implant of the present invention. In particular Figure 4A depicts a cross-sectional view of a vascular graft 34 according to the method and implant of the present invention, wherein one microencapsulated chemotherapeutic agent 10, such as an anticoagulant, is incorporated into the inner layer of the graft 36. Conversely, another microencapsulated chemotherapeutic agent 10, such as an anticoagulant antagonist, is incorporated into the outer layer of the graft 40. Alternatively, as illustrated in Fig. 4B, a single incorporation of microencapsulated chemotherapeutic agents 10 may be placed between the layers comprising the graft 38. Figs. 4C-4D illustrate further potential embodiments. For example, in Fig. 4C, microencapsulated chemotherapeutic agents 10 are only incorporated into the outer layer 40 of a vascular graft 34 in accordance with the present invention, whereas in Fig. 4D, a first microencapsulated chemotherapeutic agent 10 is incorporated into the inner layer 36 of a vascular graft 34 according to the present invention, while a second microencapsulated chemotherapeutic agent 10 is incorporated between the layers comprising the graft 38. It is to be understood that any additional potential combinations of microencapsulated chemotherapeutic agents, alone or in combination with optional carrier agents, which may be incorporated into any layers, or spaces between the layers, of a vascular or related graft are considered within the scope of this invention.

Figure 5 illustrates a cruciate ligament prosthesis 44 incorporating microencapsulated chemotherapeutic and optional carrier agents according to the method and implant of the present invention. Such prostheses are made of bundled fibers 46, composed of materials such as PTFE, and are utilized in reconstructive surgery of injured knee joints. Preferred chemotherapeutic agents include antibiotics,

such as vancomycin, which help to safeguard against threatening infections, such as staph infections, which would jeopardize the implant and surrounding tissue. Also preferred are anti-inflammatory agents, such as a nonsteroidal anti-inflammatory drug, which minimize post-surgical swelling and discomfort and expedite healing and renewal of normal function.

Illustrated in Figures 6A,B, are enlarged partial sectional views through a fiber bundle 46 of the cruciate ligament prosthesis 44 shown in Figure 5, illustrating different configurations of microparticles being present. In particular, in Fig. 6A, the individual fibers 48 comprising the bundle 46 are interwoven with a matrix of chemotherapeutic and optional carrier agent encapsulating microfibers 16 or microfibrils 16 in accordance with the present invention. Alternatively, in Fig. 6B, the fibers 48 comprising the bundle 46 are surrounded by microspheres 14 incorporating chemotherapeutic and optional carrier agents.

Illustrated in Figures 7A through 7D, are various chemotherapeutic agent release patterns which might be achieved using the principles of the present invention. The charts shown illustrate quantity or dosage of the chemotherapeutic agent released over time. In Figure 7A, three separate chemotherapeutic agents are illustrated as being released at three different substantially constant levels. For example, an antibiotic, anti-inflammatory and tissue regenerative agent may all be released at varying levels at an implantation site. In Figure 7B, three different chemotherapeutic agents are released at different times. Thus, in accordance with the previous example, the antibiotic may be released first to control post-operative infection, followed by the anti-inflammatory agent to control swelling, and finally a tissue regenerative agent to aid in healing. In Figure 7C, a

first chemotherapeutic agent is illustrated as being released very early in time and then a second chemotherapeutic agent is released at a substantially constant level for a sustained period of time. An initial high dose release of an antibiotic, followed by a sustained and lower release dose of an anti-inflammatory agent would be illustrative of such a release pattern. Finally, Figure 7D illustrates three different chemotherapeutic agents being released at different times. Such an impulse release pattern may prove particularly useful with a drug which exhibits toxic effects at sustained high dosages or whose efficacy diminishes if administered continuously over a sustained period of time.

It will be appreciated that in addition to the method and implant described above, the method of the present invention may be utilized with a wide variety of other biomedical devices, including without limitation, vascular access devices, synthetic heart valve leaflets, tendon implants, transcutaneous access devices and artificial skin.

It will be further appreciated that the particular chemotherapeutic agents and optional carrier agents utilized, as well as the dosages and durations of treatment, will be in accordance with accepted treatment. The present invention addresses the manner in which the chemotherapeutic and optional carrier agents are delivered to the local treatment site.

It is to be understood, however, that even though numerous characteristics and advantages of the invention have been set forth in the foregoing description, together with details of the structure and function of the invention, the disclosure is illustrative only, and changes may be made in detail, especially in matters of shape, size and arrangement of parts within the principle of the invention, to the full

extent indicated by the broad general meaning of the terms in which the appended claims are expressed.

CLAIMS:

1. A method for sustained, controlled delivery of chemotherapeutic agents incorporated into implants to localized treatment sites in a mammalian body, comprising the steps of:

incorporating time-release microshapes encapsulating at least one chemotherapeutic agent into a biocompatible implant so as to provide for sustained, controlled delivery of said at least one chemotherapeutic agent to a localized treatment site in a mammalian body; and

implanting said implant at said localized treatment site, wherein said time-release microshapes will begin to release said at least one chemotherapeutic agent at said localized treatment site.

2. The method of claim 1 further comprising prior to the implanting step, incorporating at least one carrier agent into said implant so as to provide for the improved cellular uptake of said at least one chemotherapeutic agent at the localized treatment site.

3. The method of claim 2 wherein the carrier agent is hyaluronic acid or a derivative thereof.

4. The method of claim 3 wherein the carrier agent is encapsulated in a time-release microshape.

5. The method of claim 3 wherein the carrier agent is mixed with the at least one chemotherapeutic agent and encapsulated in said time-release microshape prior to incorporating said time-release microshapes into said implant.

6. The method of claim 1 wherein the implanting step includes permanently implanting said

implant at said localized treatment site in a mammalian body.

7. The method of claim 1 wherein the incorporating step includes selecting a guided tissue regeneration barrier as the implant to have incorporated therein time-release microshapes encapsulating at least one chemotherapeutic agent, and wherein said tissue regeneration barrier is removed after being implanted for a predetermined period of time.

8. The method of claim 1 wherein the incorporating step includes selecting a biocompatible implant which is nonresorbable.

9. The method of claim 1 wherein the incorporating step includes selecting a biocompatible implant which is resorbable.

10. The method of claim 8 wherein the incorporating step includes selecting a biocompatible, nonresorbable implant composed of a material selected from the group consisting of polytetrafluoroethylene, dacron, proplast, polypropylene and ethers of hyaluronic acid.

11. The method of claim 9 wherein the incorporating step includes selecting a biocompatible, resorbable implant composed of cross-linked collagen or esters of hyaluronic acid.

12. The method of claim 1 wherein the incorporating step includes selecting microshapes selected from the group consisting of microspheres, microfibrils, microfibers, hollow microfibers and microsponges.

13. The method of claim 12 wherein the incorporating step includes selecting microspheres sized between approximately 10 to 700 microns in diameter or hollow microfibers having a cross-sectional diameter between approximately 100 to 1000 microns.

14. The method of claim 1 wherein the incorporating step includes selecting time-release microshapes encapsulating said chemotherapeutic agents which have time release values, thereby assuring generally continuous release of said chemotherapeutic agents over a predetermined period of time.

15. The method of claim 14 wherein the incorporating step includes mixing said chemotherapeutic agent with a polymer comprising said time-release microshape.

16. The method of claim 15 wherein the mixing step includes selecting a biocompatible, non-resorbable polymer.

17. The method of claim 15 wherein the mixing step includes selecting a biodegradable, resorbable polymer.

18. The method of claims 16 or 17 wherein the mixing step includes selecting the polymer from the group consisting of collagen, cellulosic polymers, ethylene vinyl acetate, methacrylate polymers, lactic glycolic acid polymers, polycaprolactone, polylactides, polystyrene, polycarbonate, polysulfone, polyurethane, esters of hyaluronic acid and ethers of hyaluronic acid.

19. The method of claim 1 wherein the incorporating step includes selecting microshapes for incorporation into said implants which are surrounded by

a polymeric wall or shell, thereby providing for continuous or periodic release of said chemotherapeutic agents over a predetermined period of time.

20. The method of claim 1 wherein the incorporating step includes incorporating said microshapes into said implant by extruding said microshapes into the matrix of said implant, weaving said microshapes into the matrix of said implant, mixing said microshapes with a fluid and/or gel and flowing them into the netting or weave of said implant, placing said microshapes between the layers of said implant or positioning said microshapes between said implant and an elastomer coating covering said implant.

21. The method of claim 20 wherein the fluid is hyaluronic acid and the gel is a cross-linked gel of hyaluronic acid.

22. The method of claim 1 wherein the incorporating step includes selecting the chemotherapeutic agent from the group consisting of antibacterial, antibiotic, anti-inflammatory, anticoagulant and tissue regenerative agents.

23. The method of claim 22 wherein the incorporating step includes selecting the antibacterial agent from the group consisting of bisbiguanides, fluorides, iodine, heavy metal salts and sulfonamides.

24. The method of claim 22 wherein the incorporating step includes selecting the antibiotic agent from the group consisting of vancomycin, tetracycline, penicillin, cephalosporins, erythromycin, metronidazole, neomycin and kanamycin.

25. The method of claim 22 wherein the incorporating step includes selecting the anti-inflammatory agent from the group consisting of steroidal anti-inflammatory agents and nonsteroidal anti-inflammatory agents.

26. The method of claim 25 wherein the incorporating step includes selecting the steroidal anti-inflammatory agent from the group consisting of cortisone, hydrocortisone, beta-methasone, dexamethasone and prednisolone.

27. The method of claim 25 wherein the incorporating step includes selecting the nonsteroidal anti-inflammatory agent from the group consisting of indomethacin, flurbiprofen, meclofenamic acid, ibuprofen and naproxen.

28. The method of claim 22 wherein the incorporating step includes selecting the anticoagulant agent from the group consisting of heparin, dextran, prostacyclin and prostaglandin analogues.

29. The method of claim 22 wherein the incorporating step includes selecting the tissue regenerative agent from the group consisting of fibronectin and bone morphogenic protein.

30. A surgical implant comprising a porous polytetrafluoroethylene matrix having a microstructure composed of fibers and nodes, said nodes being connected to one another by the fibers, said matrix further containing time-release microshapes encapsulating at least one chemotherapeutic agent incorporated into said porous matrix, wherein said time-release microshapes will begin to release said at least one chemotherapeutic

agent at a localized treatment site upon surgical implantation of said implant.

31. The surgical implant of claim 30 further containing at least one carrier agent incorporated into the matrix of said implant so as to provide for the improved cellular uptake of said at least one chemotherapeutic agent at the localized treatement site upon surgical implantation of said implant.

32. The surgical implant of claim 31 wherein the carrier agent is hyaluronic acid or a derivative thereof.

33. The surgical implant of claim 32 wherein the carrier agent is encapsulated in a time-release microshape.

34. The surgical implant of claim 32 wherein the carrier agent is mixed with the at least one chemotherapeutic agent and encapsulated in said time-release microshape prior to incorporating said time-release microshapes into said matrix of said implant.

35. The implant of claim 30 wherein said implant is a guided tissue regeneration barrier, vascular graft, vascular access device, heart valve leaflet, ligament prosthesis, tendon prosthesis, transcutaneous access device, reconstructive patch, urethral prosthesis or artificial skin.

36. The implant of claim 35, wherein said barrier is constructed of a biodegradable, resorbable material.

37. The implant of claim 36, wherein said biodegradable, resorbable material is cross-linked collagen or an ester of hyaluronic acid.

38. A surgical implant comprising a biocompatible matrix, said matrix further containing time-release microshapes encapsulating at least one chemotherapeutic agent incorporated into said matrix, wherein said time-release microshapes will begin to release said at least one chemotherapeutic agent at a localized treatment site upon surgical implantation of said implant.

39. The surgical implant of claim 38 further containing at least one carrier agent incorporated into the matrix of said implant so as to provide for the improved cellular uptake of said at least one chemotherapeutic agent at the localized treatment site upon surgical implantation of said implant.

40. The surgical implant of claim 39 wherein the carrier agent is hyaluronic acid or a derivative thereof.

41. The surgical implant of claim 40 wherein the carrier agent is encapsulated in a time-release microshape.

42. The surgical implant of claim 40 wherein the carrier agent is mixed with the at least one chemotherapeutic agent and encapsulated in said time-release microshape prior to incorporating said time-release microshapes into said matrix of said implant.

43. The implant of claim 38 wherein the biocompatible matrix is nonresorbable.

44. The implant of claim 38 wherein the biocompatible matrix is resorbable.

45. The implant of claim 43 wherein said biocompatible, nonresorbable material is polytetrafluoroethylene, dacron, proplast, polypropylene or an ether of hyaluronic acid.

46. The implant of claim 44 wherein said biocompatible, resorbable material is cross-linked collagen or an ester of hyaluronic acid.

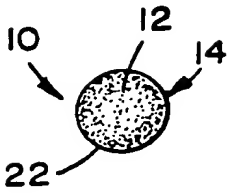


FIG. 1A

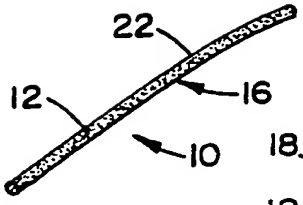


FIG. 1B

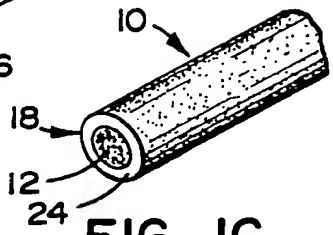


FIG. 1C

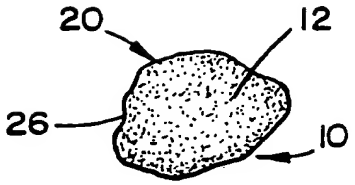


FIG. 1D

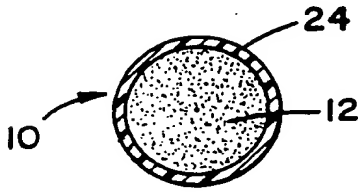


FIG. 2A

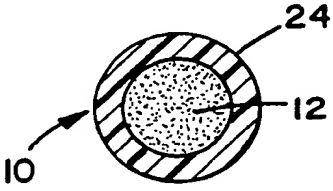


FIG. 2B

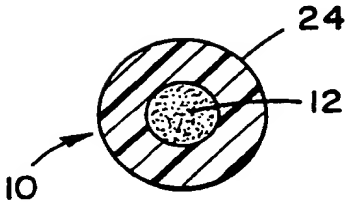


FIG. 2C

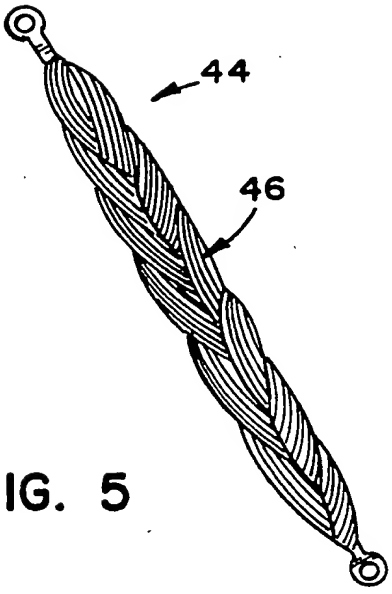


FIG. 5

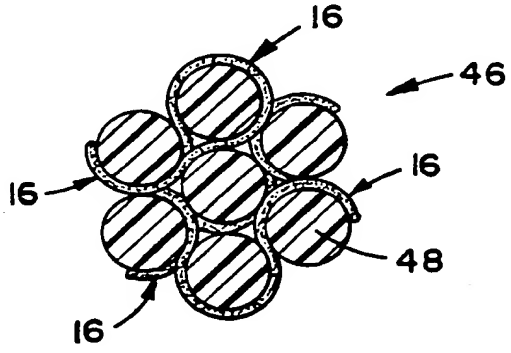


FIG. 6A

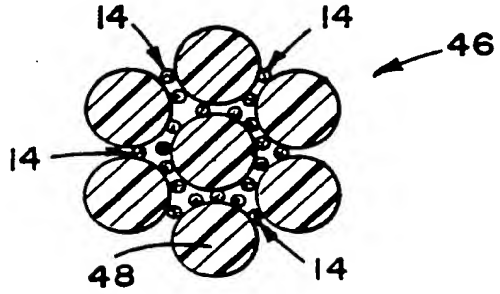
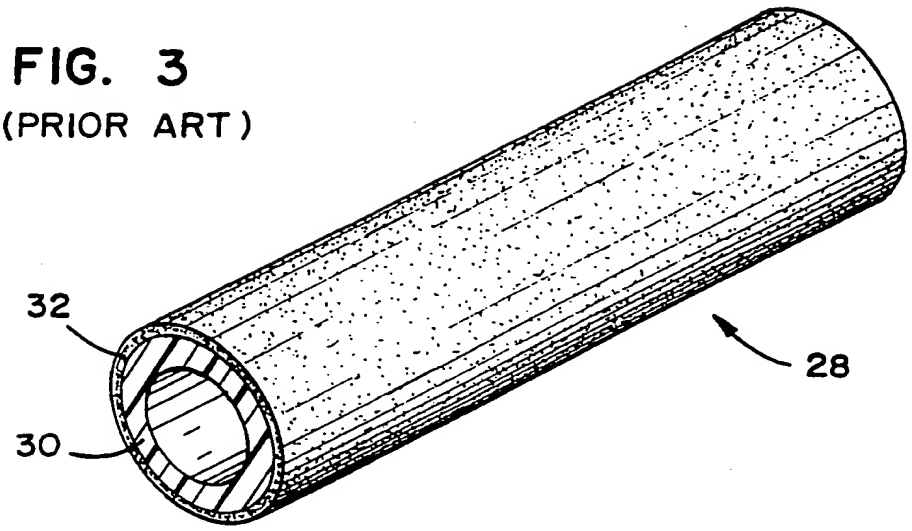


FIG. 6B

FIG. 3
(PRIOR ART)



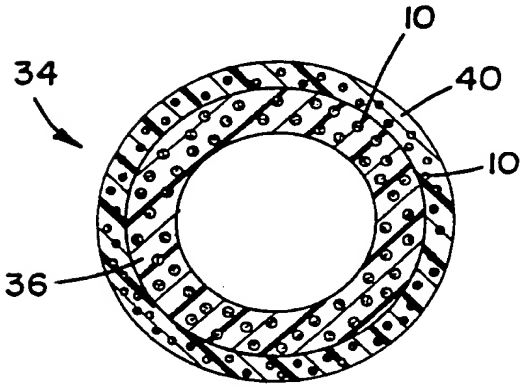


FIG. 4A

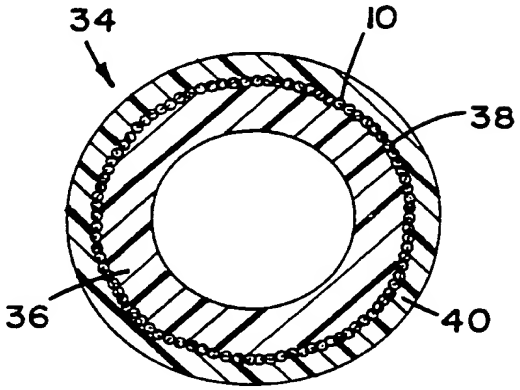


FIG. 4B

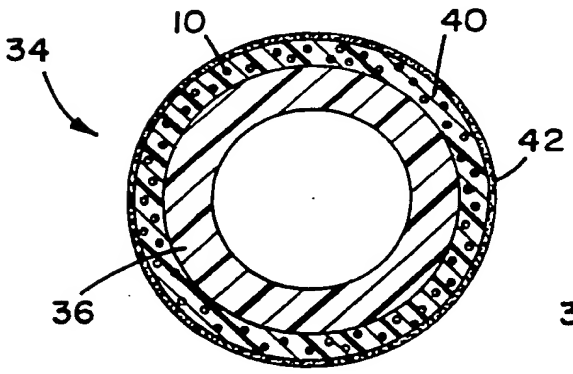


FIG. 4C

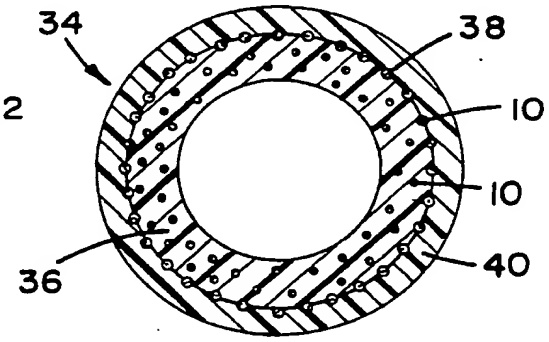


FIG. 4D

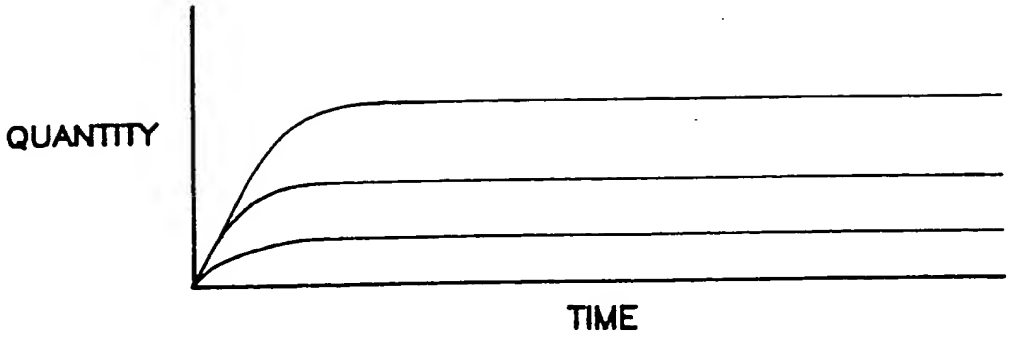


FIG. 7A

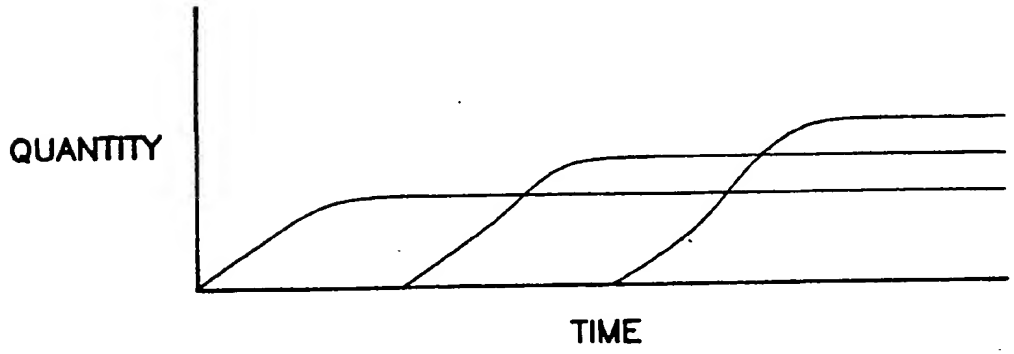


FIG. 7B

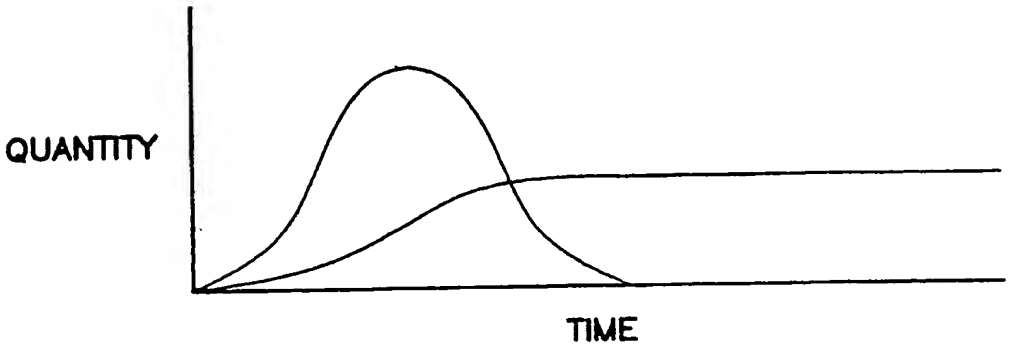


FIG. 7C

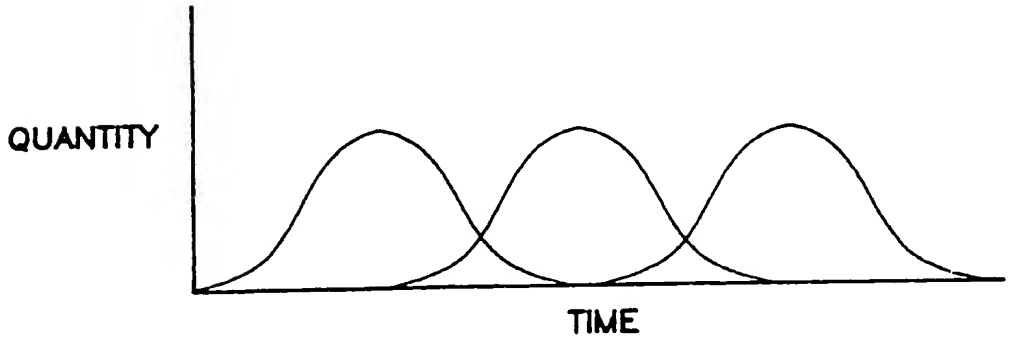


FIG. 7D

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/02784

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/22 A 61 K 9/52 A 61 L 27/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	WO,A,8706129 (DARATECH) 22 October 1987, see claims 1-5,7-10; page 2, lines 14-19,26-27; page 3, lines 10-14,22-27	30-32, 34,38-39,42, 44
A	GB,A,2103927 (C.S.I.R.-INDIA) 2 March 1983, see claims 1,8,10,21	30,34, 38,39, 42,44
A	EP,A,0216453 (FIDIA) 1 April 1987, see claims 1,15,19,24-27,30	30,32, 38,40, 44,46
A	GB,A,2033232 (SUMITOMO) 21 May 1980, see claims; page 1, lines 83-86; page 2, lines 85-90 (cited in the application)	30,31, 35,38, 39,43, 45

-/-

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26-08-1991	24 SEP 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0293090 (BAXTER TRAVENOL) 30 November 1988, see claims 1,3-6,17,24-26 (cited in the application) ---	30,35, 43,45
P,A	EP,A,0406665 (G. BROTZU) 9 January 1991, see claims; column 2, lines 16-18 -----	30,35, 38,43, 45

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 1-29 because they relate to subject matter not required to be searched by this Authority, namely:
See PCT-Rule 39.1 (iv): methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3 ☐ No required additional search fees were timely paid by the applicant Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee

Remark on Pr test

☐ The additional search fees were accompanied by applicant's protest

☐ No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9102784 SA 47905

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 8706129	22-10-87	AU-A-	7237087	09-11-87
		EP-A-	0265457	04-05-88
		JP-T-	1500034	12-01-89
GB-A- 2103927	02-03-83	None		
EP-A- 0216453	01-04-87	AU-B-	591501	07-12-89
		AU-A-	5983686	26-02-87
		JP-A-	62064802	23-03-87
		US-A-	4965353	23-10-90
		US-A-	4851521	25-07-89
GB-A- 2033232	21-05-80	JP-C-	1394410	11-08-87
		JP-A-	55054951	22-04-80
		JP-B-	60037735	28-08-85
		AU-B-	528494	28-04-83
		AU-A-	5169579	24-04-80
		BE-A-	879356	01-02-80
		CA-A-	1140705	08-02-83
		DE-A-	2941281	24-04-80
		FR-A,B	2439005	16-05-80
		NL-A-	7907532	22-04-80
		SE-B-	443288	24-02-86
		SE-A-	7908446	19-04-80
		US-A-	4321711	30-03-82
EP-A- 0293090	30-11-88	US-A-	4816339	28-03-89
		JP-A-	1046468	20-02-89
EP-A- 0406665	09-01-91	AU-A-	5864690	10-01-91
		JP-A-	3041948	22-02-91